## REMARKS

Claims 1-2 and 4-41 are pending, applicants having previously canceled claim 3. Applicants acknowledge with appreciation the Examiner's withdrawal of the claim rejections under 35 U.S.C. §112 and 35 U.S.C. §102. In the Final Office Action now under reply, the claims have been rejected as follows:

(1) claims 1-2, 4-10, 12-31, 34-35, 37-38, and 40-41 are rejected under 35 U.S.C. §103(a) as unpatentable over Kim et al., US 5,455,044 ("Kim") in view of Penners et al., US 6,306,439, ("Penners");

(2) claim 11 is rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners and further in view of Chen et al., *Proc. Nat. Acad. Sci.*, 2002, 99(13), 9031-9036 ("Chen");

(3) claim 32 is rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners, further in view of Chen, and further in view of Hatcher et al., *Soc. For Neurosciences*, 19th Annual Meeting, Abs. #236.4, Oct. 23-28, 1999 ("Hatcher"); and

(4) claims 36 and 39 are rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners, and further in view of Russell et al. *Bone Marrow Transplantation*, 1999, 24, 1177-1183 ("Russell").

Applicants note that the status of claim 33 is not mentioned in the Detailed Action, but is included with the rejected claims on the Office Action Summary.

The rejections are overcome in part by the amendments made herein, and are otherwise traversed for at least the reasons set forth below.

***Claim Amendments***

Claim 1 has been amended to recite that the biocompatible composition is suitable for administration to the cerebrospinal fluid of a subject. Support for this amendment is provided, for example, in the original specification at page 3, lines 30-31. Accordingly, no new matter is added by these amendments.

***First rejection under 35 U.S.C. §103(a)***

Claims 1-2, 4-10, 12-31, 34-35, 37-38, and 40-41 are rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners. The Examiner cites the reasons set forth in the Office Action dated June 2, 2006 ("the June 2006 Action"). This rejection is traversed.

The compositions and methods described by the pending claims are not obvious extensions of the technologies described by Kim, Penners, or any purported combination of Kim and Penners. The skilled artisan would have no reason to combine the teachings of Kim with those of Penners, but would, in fact, have reason not to combine such teachings. These conclusions are set forth and discussed in Applicant's response dated December 4, 2006 ("the December 2006 response"). Further explanation of applicant's reasoning, as well as additional evidence and arguments, are set forth below.

In the June 2006 Action, it is stated that Kim lacks the teachings of a specific buoyancy agent, and that Penners provides such teachings. It is also stated that Penners teaches that the gas-forming substances in his composition evolve non-toxic gases upon contact with water. The June 2006 Action concludes that it would have been obvious to a person of ordinary skill at the time of the instant invention to combine the teachings of Kim and Penners.

As pointed out in the December 2006 response, and as supported by the declaration under 37 C.F.R. §1.132 by Dr. Tim Maher (submitted herewith as Exhibit A), combining the teachings of Kim with those of Penners would not have been obvious to the skilled artisan. In fact, the skilled artisan would have been *highly discouraged* from making such a combination. Kim relates to compositions suitable for delivery to the central nervous system (CNS) of a patient, while Penners relates to compositions suitable for delivery to the gastrointestinal (GI) tract of a patient. Because of the physiological differences between the CNS and the GI tract, compositions suitable for administration to one are not necessarily suitable for administration to the other. The compositions described by Penners and cited by the Examiner involve the degradation of hydrogen carbonates, a reaction that produces carbon dioxide and hydroxide ion. The December 2006 response and the declaration of Dr. Maher establish that the skilled artisan would have been discouraged from combining the teachings of the cited references at least because the hydroxide ion produced by the degradation reaction described in Penners has the potential to cause serious adverse side effects when applied to compositions intended to be administered to the CNS. In essence, the highly sensitive nature of the CNS preclude the use of a

many of compositions that are designed for administration to the GI tract. There is therefore a high probability that the skilled artisan would have been motivated to *avoid* combining the teachings of Kim with the teachings of Penners, as evidenced by Dr. Maher's Declaration and the arguments set forth in the December 2006 response.

In addition, Kim does not, in fact, teach that the specific gravity or buoyancy of polymer particles within the cerebrospinal fluid (CSF) may be varied. Kim teaches dispersion systems that contain a dispersed phase (e.g., beads, micelles, microspheres, etc.) and a water phase. Kim states that "the density of the dispersion system can be modified by altering the specific gravity to make the dispersion hyperbaric or hypobaric." By this statement, Kim is teaching modification of the density of the dispersion as a whole. Such modification is practically accomplished by altering the density of the *water phase* (as opposed to the density of the particles of the *dispersed phase*). This distinction is supported by the examples of additives cited by Kim as useful for modifying the density of the dispersion material: iohexol, iodixanol, metrizamide, sucrose, trehalose, glucose, or other biocompatible molecules with high specific gravity. All of these additives are highly water soluble, indicating that Kim is describing modification of the density of the water phase.

The distinction between modifying the density of the water phase, as taught by Kim, and modifying the density of the dispersed phase, as taught by the present application, is of vital importance. The density of the dispersed phase is modified in the present application in order to adjust the buoyancy of the polymer particles *within the CSF*. In the systems taught by Kim, however, the water phase of the dispersion system is quickly absorbed into the surrounding liquid (i.e., the water phase is simply a carrier for the particles) upon administration to a patient's CSF. Therefore, adjusting the density of the water phase, as described by Kim, may affect the buoyancy of the particles within the *water phase*, but would have little or no effect on the buoyancy of the particles *within the CSF*. In other words, Kim provides a method for adjusting the density of the dispersion systems during their preparation (i.e., in vitro) rather than during their administration (i.e., in vivo). Kim neither teaches nor suggests a composition that is controllably buoyant *within the cerebrospinal fluid*, as recited in the instant claim 1.

For at least the foregoing reasons, the combination of Penners and Kim do not render obvious claims 1-2, 4-10, 12-31, 34-35, 37-38, and 40-41, and applicants respectfully request withdrawal of the rejection.

***Second rejection under 35 U.S.C. §103(a)***

Claim 11 stands rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners and further in view of Chen. The Examiner states that both Kim and Penners lack the teaching of a biocompatible composition wherein the therapeutic agent is selected from the group of inosine, citicholine, superoxide dismutase, and dextrophan, and that this deficiency is cured by the teachings of Chen (Action of June 2, 2006, page 13). This rejection is traversed.

The merits of the combination of Kim and Penners are discussed above. In summary, one of ordinary skill in the art would find no motivation to combine the teachings of Penners with Kim, at least for the reason that the compositions of Penners would generate byproducts that are potentially toxic to the CNS and are therefore unsuitable for administration to the CSF.

Regardless of the therapeutic agents that are employed, the teachings of Chen do not provide the motivation that would be needed to combine the teachings of Kim with the teachings of Penners. Chen is directed to the effects of inosine on rats suffering from certain types of strokes. Chen does not address biocompatible compositions suitable for administration to the cerebrospinal fluid of a subject comprising a plurality of polymer particles, as claimed. Therefore, Chen does not address the deficiencies of either Kim or Penners, or the combination of Kim with Penners as described above, with respect to claim 1 (and claims dependent thereon, including claim 11). Any combination of Chen with Kim or Penners (or both) fails to teach the claimed invention; accordingly, applicants respectfully request withdrawal of the rejection.

***Third rejection under 35 U.S.C. §103(a)***

Claim 32 stands rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners, further in view of Chen, and further in view of Hatcher. The Examiner contends that Kim, Penners, and Chen lack the teaching of a composition comprising both inosine and citicholine as therapeutic agents, and that this deficiency is cured by the teachings of Hatcher (Action of June 2, 2006, page 14). This rejection is traversed.

The merits of the combination of Kim, Penners, and Chen are discussed above. In summary, one of ordinary skill in the art would find no motivation to combine the teachings of Penners with Kim, at least for the reason that the compositions of Penners would generate byproducts that are potentially toxic to the CNS and are therefore unsuitable for administration to

the CSF. Furthermore, Chen does not provide the motivation that would be required to combine the teachings of Kim with those of Penners.

Regardless of the therapeutic agents that are employed, the teachings of Hatcher do not provide the motivation that would be needed to combine the teachings of Kim with those of Penners and with those of Chen. Hatcher is directed to the neuroprotective effect of CDP-choline in hippocampal $CA_1$ region after transient ischemia of gerbils (see Abstract). Hatcher does not address biocompatible compositions suitable for administration to the cerebrospinal fluid of a subject comprising a plurality of polymer particles, as claimed. Therefore, Hatcher does not address the deficiencies of Kim, Penners, Chen, or any combination thereof, as described above, with respect to claim 12 (and claims dependent thereon, including claim 32). Accordingly, applicants respectfully request withdrawal of the rejection.

***Fourth rejection under 35 U.S.C. §103(a)***

Claims 36 and 39 stand rejected under 35 U.S.C. §103(a) as unpatentable over Kim in view of Penners, and further in view of Russell. The Examiner states that Kim and Penners lack the teaching of living cells as therapeutic agents, and that this deficiency is cured by the teachings of Russell (Action at page 16). This rejection is traversed.

The merits of the combination of Kim and Penners are discussed above. In summary, one of ordinary skill in the art would find no motivation to combine the teachings of Penners with Kim, at least for the reason that the compositions of Penners would generate byproducts that are potentially toxic to the CNS and are therefore unsuitable for administration to the CSF.

Regardless of the therapeutic agents that are employed, the teachings of Russell do not provide the motivation that would be needed to combine the teachings of Kim with the teachings of Penners. Russell is directed to the treatment of leukemia using living cells as therapeutic agents. Russell does not address biocompatible compositions suitable for administration to the cerebrospinal fluid of a subject comprising a plurality of polymer particles as claimed. Therefore, Russell does not address the deficiencies of either Kim or Penners, or the combination of Kim with Penners as described above, with respect to claims 1 or 22 (and claims dependent thereon, including claims 36 and 39). Any combination of Russell with Kim or Penners (or both) fails to teach the claimed invention; accordingly, applicants respectfully request withdrawal of the rejection.

## CONCLUSION

Applicants submit that the claims of the application are in condition for allowance. Applicants respectfully request withdrawal of the rejections, and prompt issuance of a notice of allowance. If the Examiner has any questions concerning this communication, or would like to discuss the application, the art, or other pertinent matters, a telephone call to the undersigned would be welcomed.

Respectfully submitted,

By: 

Isaac M. Rutenberg
Registration No. 57,419
c/o MINTZ LEVIN
1400 Page Mill Road
Palo Alto, California 94304-1124
(650) 251-7700 Telephone
650) 251-7739 Facsimile
**Customer No. 23,980**

# Exhibit A

**Declaration under 37 C.F.R. §1.132 by Dr. Timothy Maher**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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|---|---|---|---|
| APPLICANTS: | Pratt et al. | | |
| ASSIGNEE: | seaCoast NeuroScience, Inc. | | |
| SERIAL NUMBER: | 10/723,626 | EXAMINER: | ALSTRUM ACEVEDO, James Henry |
| FILING DATE: | November 26, 2003 | ART UNIT: | 1616 |
| FOR: | BUOYANT POLYMER PARTICLES FOR DELIVERY OF THERAPEUTIC AGENTS TO THE CENTRAL NERVOUS SYSTEM | | |

Boston, Massachusetts

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

**DECLARATION of TIMOTHY MAHER UNDER 37 C.F.R. §1.132**

I, TIMOTHY MAHER, PH.D., DO HEREBY DECLARE:

1. I am a full professor of pharmacology at the Massachusetts College of Pharmacy and Health Sciences ("MCPHS") and have had 26 years of experience performing research on small animals (rats, mice, hamsters) involving neurochemical, neurobehavioral, and neuropharmacologic studies. My expertise is in stereotaxic surgery, in vivo microdialysis, neurobehavioral models of neurological diseases (including stroke, spinal cord injury, Parkinson's disease, Alzheimer's, Huntington's, and metal toxicity), as well as in analytical procedures including HPLC and enzymatic assays. I have also performed contract research under a for-profit company owned by MCPHS (Longwood Pharmacology Research, Inc) where I served as President and CEO. I hold a Ph.D. in pharmacology, and I have published over one-hundred articles in peer-reviewed scientific journals.

2. I have recently reviewed United States Patent Application number 10/723,626 ("the '626 application"), which is entitled "BUOYANT POLYMER PARTICLES FOR DELIVERY OF THERAPEUTIC AGENTS TO THE CENTRAL NERVOUS SYSTEM," and which was filed in the United States Patent and Trademark Office on November 26, 2003.

3. I understand that the '626 application has been assigned to seaCoast NeuroScience, Inc. I am not employed by seaCoast, nor do I hold stock in seaCoast at the present time. I have previously collaborated with seaCoast employees in the form of preparing research grant applications. My interests in collaborating with seaCoast are generally academic in nature - I hope to obtain grant money to support my research and research projects with seaCoast. I have not assisted seaCoast with any grant applications that are pending at this time.

4. I have been informed that during prosecution of the '626 application, original claim 3 was canceled, and that prosecution of claims 1, 2, and 4-41 is proceeding. I understand that the claims relate to polymer particles that contain a therapeutic agent and a buoyancy agent.

5. I have been informed that the examiner who is examining the '626 application at the United States Patent Office has rejected claims 1-2, 4-10, 12-31, 34-35, 37-38, and 40-41 under 35 U.S.C. §103(a) as obvious over Unites States Patent No. 5,455,044 to Kim et al. ("the Kim patent") in view of United States Patent No. 6,306,439 to Penners et al. ("the Penners patent"). I have recently reviewed the Examiner's arguments supporting this rejection as set forth in the Office Action dated June 2, 2006. I have also recently reviewed the relevant portions of the disclosures of the Kim patent and the Penners patent.

6. The Kim patent is directed primarily to treating a neurological disorder by administration to the cerebrospinal fluid (CSF) of a therapeutic agent in a dispersion system which allows the therapeutic agent to persist in the cerebro-ventricular space. The dispersion systems taught by the Kim patent comprise particles that are dispersed in a pharmaceutical buffer, and are preferably administered to the patient by injection (e.g., directly into the CSF by intralumbar puncture). As I would expect for a pharmaceutical formulation designed to be injected directly into the CSF of a patient, the Kim patent states that the materials used in the formulations are typically sterilizable, nontoxic, and biodegradable.

7. According to the teachings of the Kim patent, the density of the dispersion systems can be modified by altering the specific gravity to make the dispersion hyperbaric or hypobaric. Example materials for altering the specific gravity, as provided by the Kim patent, are iohexol, iodixanol, metrizamide, sucrose, trehalose, glucose, or other biocompatible molecules with high specific gravity.

8. The Penners patent is directed primarily to pharmaceutical formulations intended to be administered orally. The administration forms taught in the Penners patent differ from conventional oral dosage forms in that they have a relatively long gastric residence time. The Penners patent teaches that a relatively long gastric residence time may be obtained by incorporation of a gas-forming mixture. Examples of suitable gas-forming agents are set forth in column 5, lines 5-15 of the Penners patent. These are hydrogen carbonates such as sodium hydrogen carbonate, and may be used alone or in combination with acids.

9. The hydrogen carbonates described in the Penners patent decompose upon contact with water or gastric fluid. The products resulting from such decomposition are carbon dioxide ($CO_2$) and hydroxide ion ($OH^-$). This decomposition reaction of hydrogen carbonates is widely

known to practitioners in medicinal chemistry and synthetic chemistry. Hydroxide ion is a strongly basic substance.

10. The formulations described in the Penners patent are designed and intended for use in the gastrointestinal (GI) tract. The GI tract is subject to a wide variety of external stimuli, most notably the solids and liquids encountered in the course of normal metabolic regulation (e.g., the processes of eating and drinking). Accordingly, the GI tract is designed to tolerate wide variations in pH. Furthermore, it is common practice to administer to the GI tract compositions comprising a hydrogen carbonate (e.g., antacid medications such as common baking soda); the hydroxide ions generated by the decomposition reaction of such compositions is often beneficial for regulating the pH of the GI tract.

11. In contrast to the GI tract, the central nervous system (CNS) of a patient is quite sensitive to external stimuli. Under normal circumstances, the CNS contains CSF, which is stringently regulated to prevent the introduction of toxic substances into the CNS. For example, the pH of the CSF is typically maintained at about 7.35, and unlike for the GI tract, wide fluctuations in pH of the CSF are uncommon. In fact, such fluctuations have the potential of being severely harmful to the organs of the CNS, and may further disrupt physiological processes such as signal transmission along/among nerve cells.

12. In general, the CNS is highly sensitive and susceptible to damage from toxic substances - more so than the GI tract. Furthermore, administration of pharmaceutical formulations directly to the CSF is generally avoided for any formulations that contain hazardous or potentially hazardous substances. The threshold for determining whether a substance will be hazardous is lower for the CNS than for the GI tract. Accordingly, drug formulations and related technologies that are suitable for administration to the GI tract are not necessarily suitable for administration to the CNS.

13. In consideration of the above, prior to November 26, 2003 I would not have looked to the Penners patent for guidance in modifying the formulations taught in the Kim patent. The methods for generating a gas that are described in the Penners patent also produce byproducts potentially toxic to the CNS. Had it been suggested to me to incorporate the gas-forming agents described in the Penners patent into pharmaceutical formulations intended to be delivered directly to the CSF, I would have been highly concerned that the gas-forming agents would produce toxic byproducts and result in harmful side effects for a patient receiving treatment with such formulations.

14. Even though the "normal" pH of the CSF is slightly above 7.0, and the CSF may therefore include a nominal concentration of hydroxide ion, the likelihood of adverse reactions caused by introducing additional hydroxide ion into the CSF would have prevented me from looking to the Penners patent for guidance in modifying the formulations taught in the Kim patent.

15. The Examiner has suggested that the amount of hydroxide ion generated by a hydrogen carbonate is too small to adversely affect the pH of the CSF. Even if this were proved to be true (i.e., by experimentation) for specific formulations administered to specific patients, the

general likelihood of adverse reactions would have prevented me from consulting the Penners patent for guidance in modifying the formulations of the Kim patent.

16. The Examiner has suggested that hydroxide ion generated by the decomposition of a hydrogen carbonate could be mitigated by the inclusion, for example, of an acid in the formulation. Even if such a formulation could be developed, balancing the acid-base reactions involved would likely require significant and extensive experimentation in order to ensure that the closely regulated environment of the CSF does not diverge from acceptable physiologically conditions as a result of administration of such a formulation. Because of the delicate nature of the CSF, therefore, the low expectation of success for such a formulation would have prevented me from consulting the Penners patent for guidance in modifying the formulations of the Kim patent.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under § 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Date: 5/30/07 Signed: _____
Timothy Maher, Ph.D.